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REVIEW

Organochlorine compounds and estrogen-related cancers in women

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The organochlorines, a diverse group of some 15,000 compounds, have been implicated increasingly as being harmful to humans. Some congeners of DDT and PCB elicit very weak to weak estrogenic responses in animals, while the dioxin TCDD and related compounds have antiestrogenic properties. This review summarizes the evidence regarding whether certain organochlorine compounds, usually as persistent food-chain contaminants, increase the risk of breast and endometrial cancers through their estrogenic potential. In humans, neither ecologic data nor occupational studies provide clear support for an association between organochlorine exposure and the occurrence of these cancers. In our summary analysis of occupational exposure, the rate ratio of breast cancer for exposed *cf* unexposed women was 0.84 (95 percent confidence interval [CI] = 0.50-1.33) for PCBs and 1.08 (CI = 0.68-1.58) for TCDD. Similarly, effect estimates close to unity were found in summary analysis of breast cancer case-control studies regarding levels of DDE and PCB in adipose tissue or serum. In two recent nested case-control studies using stored specimens, the odds ratio per standard deviation increase in serum p,p'-DDE was 1.27 (CI = 0.95-1.69). Although estrogenic effects of certain organochlorine compounds should be easier to detect on the endometrium, we know of no analytic epidemiologic studies of endometrial cancer published to date. We conclude that available data do not indicate that organochlorines will affect the risk of these two cancers in any but the most unusual situation. *Cancer Causes and Control 1995, 6, 551-566*

Key words: Breast cancer, endometrial cancer, estrogens, organochlorine compounds.

Introduction

The purpose of this review is to evaluate the existing evidence that exposure to organochlorine compounds may increase the risk of breast cancer and endometrial cancer through their estrogenic potential. The organochlorines are a diverse group of some 15,000 compounds and virtually nothing can be concluded about these

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compounds as a class. Therefore, our review will focus on the most well-known and intensely studied organochlorine compounds that have been involved frequently in public debate. This limited group of persistent compounds – for the sake of simplicity referred to here as 'organochlorines' – includes the PCDDs (polychlorinated dibenzo-p-dioxins), notably TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), the PCBs (polychlorinated biphenyls) and chlorinated pesticides. In this latter group is DDT [1,1,1-Trichloro-2-2-bis(4-chlorophenyl)ethane] with its metabolites. Special attention will be given to epidemiologic evidence, but laboratory data and results from experimental studies in animals also will be taken into account. The toxicologic background has been more extensively discussed in a concomitant paper.[1]

The PCB compounds and chlorinated pesticides were introduced commercially for use as flame retardants, insecticides, or fungicides, while PCDDs and polychlorinated dibenzofurans (PCDFs) are formed as byproducts and contaminants in the production of various chlorinated compounds and in combustion processes. The manufacture of PCBs and most of the chlorinated pesticides, including DDT, has been banned and their use has been restricted severely in the Western world since the early 1970s. However, since these compounds are environmentally stable and highly lipophilic, food chain contamination still exists. Although air and water pollution contribute to the human body burden, contaminated foods (particularly animal products) primarily account for human exposure. These substances generally are eliminated slowly from the body, raising concerns about the effects of chronic, low-level exposure from the food chain.

Experimental evidence

Estrogenic effects

In this review, 'estrogenicity' denotes the property of producing biologic responses comparable to those of endogenous estrogens, such as increased uterine weight and vaginal epithelial cornification. Several experimental studies[2-6] have shown that o,p'-DDT binds to the estrogen receptor and in all essential aspects mimics the action of 17β-estradiol. In terms of estrogenic properties; however, organochlorine compounds are all at least three orders of magnitude less potent than 17β-estradiol. The effects reported include increased uterine wet weight and glycogen content, enzyme induction, increased uterine DNA synthesis and cell proliferation, and precocious puberty in female animals. Unequivocal data with regard to structure-activity relationships are not available, but several studies[2,5,6] suggest that both p,p'-DDT and p,p'-DDE have considerably weaker estrogenic activity than o,p'-DDT and perhaps no activity at all. Other organochlorine compounds, including chlordecone, demethylated metabolites of methoxychlor, as well as certain of the 209 different PCB congeners and PCB mixtures, have also been shown to elicit estrogenic responses qualitatively similar to those of o,p'-DDT.[2,6-8]

Antiestrogenic effects

Both *in vivo* and *in vitro* studies show that TCDD and related compounds exhibit a broad spectrum of antiestrogenic responses.[9-13] These effects include decreased incidence of spontaneous breast tumors, decreased uterine wet weight, decreased uterine peroxidase activity, decreased levels of estrogen and progesterone uterine receptors, and inhibition of a variety of other estrogen-induced responses. Alterations in the metabolism of 17β-estradiol could be responsible for some of the antiestrogenic effects of TCDD at relatively high doses, although there is no clear evidence to support that hypothesis. Available data suggest that TCDD exerts most of its action through binding to a specific receptor, the aryl hydrocarbon receptor (AhR). The AhR ligand complex then binds to a xenobiotic response element on the estrogen receptor gene and down-regulates synthesis of estrogen receptor mRNA.[14] The possible mechanisms for interference of PCDDs/PCDFs with estrogen regulation has been dealt with in other reviews.[1,15]

Carcinogenic effects

Carcinogenic effects of halogenated aromatic hydrocarbons have been demonstrated most frequently in animal studies of exposure to the dioxin congener TCDD, to mixtures of 1,2,3,6,7,8-hexachlorodibenzo dioxin and 1,2,3,7,8,9-hexachlorodibenzo dioxin, and to commercial PCB products. TCDD is considered the most toxic of the dioxin-like organochlorine compounds, and it has been used as a prototype to investigate the carcinogenic potential of other members of this class of chemicals.[16-19] The toxicity of organochlorine compounds varies according to the structure, and the degree of chlorination, of individual congeners.[20] Certain PCB, PCDD, and PCDF isomers are retained longer in tissues and are believed to be the carcinogenic components of mixtures.[21,22] Thus, it is crucial to establish the specific isomeric composition of mixtures being evaluated for carcinogenicity in humans.[23]

In animal carcinogenicity studies, the liver is the primary target organ following prolonged periods of absorption of toxic doses of TCDD,[16,24-26] PCBs,[27-29] and DDT.[30,31] TCDD exposure also increases the

incidence of tumors of the bile duct, skin, lung, palate, tongue, stomach, and thyroid.[9,26] In contrast, a reduced incidence of tumors of the pancreas and adrenal gland, as well as a dose-related decrease in tumors of estrogen-sensitive organs in female rats given the highest TCDD-dose of 0.1 μg/kg/day, has been reported.[9] Specifically, a decreased incidence of endometrial hyperplasia, subcutaneous mammary gland tumors, and pituitary adenomas was noted, suggesting that TCDD may act through hormonal mechanisms. The reproductive organs of male rats appeared to be unaffected by the given dose levels. Several studies also have demonstrated antitumor or inhibitory effects on tumorigenesis by PCBs. One study[28] indicated a lower incidence of parafollicular cell tumors of the thyroid and of granulosa theca cell tumors of the ovary in PCB-treated rats than in controls. Two studies[32,33] have shown that the PCB mixture Aroclor 1254 inhibits, in a dose-related manner, tumor growth in rats inoculated with a transplantable tumor.

Few studies of estrogen-related tumors caused by exposure to organochlorine compounds are available. In a two-stage tumor promotion study utilizing 2-acetoamidophenanthrene as initiating agent, p,p'-DDT of unknown purity in the diet at a concentration of 500 ppm (corresponding to an intake level of 25 mg/kg/day) to male Sprague-Dawley rats promoted the growth of mammary tumors.[34] No female rats were used. Only one dose level was used in the study, and the tumor-promoting effect of DDT was expressed mainly as a shortened latency period to the occurrence of tumors. However, in female Sprague-Dawley rats, 100 ppm p,p'-DDT in the diet decreased DMBA-induced mammary tumor and leukemia incidence while increasing the latency period as well as animal survival.[35]

The estimation of human risk in environmental assessments of selective organochlorines has been based primarily on extrapolation from carcinogenicity studies in experimental animals, rather than on documented human health effects. Federal agencies in the United States extrapolate low-dose risk of TCDD exposure in humans from animal tumor data obtained at high doses (usually 100,000 times higher). This non-threshold, linearized multistage model for estimating human cancer risk[36] assumes that TCDD behaves as a tumor initiator, which disregards the fact that most mutagenicity and carcinogenicity data suggest that TCDD is nongenotoxic and induces tumors in animals through a promotional mechanism.[27,37,38] A biologically based model for the risk assessment of receptor-mediated, nonmutagenic carcinogens may be more appropriate.[36] Gold *et al*[39] used the human-exposure/rodent-potency (HERP) index, which ranks possible cancer hazard, to estimate human risk at low dose for natural and synthetic chemicals contained in the human diet. They concluded that naturally occurring carcinogens in typical portions of common foods present a greater risk than residues of synthetic pesticides or environmental pollutants.

General population exposure

The organochlorine chemicals discussed in this paper are, in general, lipophilic and relatively persistent in the environment; as indicated, food is usually the main exposure route for humans. Once in the body, they generally accumulate in fat and are only slowly excreted. Among women, lactation is a principal route of excretion, but organochlorines are also eliminated through urinary and fecal routes.[40]

Studies of human organochlorine exposure have been conducted most extensively among populations with known or presumed occupational or accidental exposures. However, most people are exposed to much lower levels from nonoccupational sources, as documented by analyses of food, human blood, adipose tissue, and breast milk. While such analyses provide estimates of human exposure burden, their generalizability often is impaired by small sample size, non-random sampling, and limited geographic representation. Even when samples are large and representative of underlying populations, variations in specimen collection, analytic approaches and reporting hinder comparisons of study results.[40,41]

In the US, population-based surveys provide data with fairly consistent measurement methodology over time, facilitating generalizations about exposure patterns in that country.[41-44] PCBs, DDT and metabolites, hexachlorobenzene (HCB) and chlordane metabolites were found in almost all subjects sampled during the 1970s, and about 75 percent of individuals also had detectable levels of PCDDs/PCDFs. Fat levels of DDT were much higher than those of any of the other chemicals. For most of these organochlorine compounds, there was a fairly consistent pattern of increasing body burdens with advancing age. This is likely to have been the consequence of two factors: the accumulation of exposure over longer time periods, as well as the fact that older individuals probably lived through periods of heavier environmental contamination. For some organochlorines (*e.g.*, DDT and metabolites and PCBs), men had slightly lower fat concentrations than women. Similarly, non-Whites had somewhat higher levels of certain of these chemicals (*e.g.*, DDT and metabolites and PCBs) relative to Whites. There has been a decline from the early 1970s onwards in the body burden of DDT and metabolites,

PCBs, hexachlorocyclohexane (HCH), and HCB, but apparently no decrease in levels or frequency of detection of chlordane metabolites.[41,44]

Although differences in metabolism of organochlorines may affect individual burden,[41] body levels are driven largely by differences in exposure. Since use of the chemicals in the US was broadly similar to that in many industrialized countries (with marked decreases in population exposure after the early 1970s), [41] it can be assumed that similar trends and differences in body burden also would hold in other industrialized countries. However, some of the chemicals remain in use in developing countries and as expected, body burdens are higher. [38]

Carcinogenicity in humans

Ecologic data

Breast cancer. It is possible to examine potential parallels between breast cancer incidence and patterns of use of DDT, a putative estrogenic agent that was also one of the earliest and most extensively used organochlorine pesticides. Within the US, time trends in breast cancer incidence do not provide substantial evidence of a relationship with DDT exposure. The last two decades have witnessed a modest increase in the incidence of breast cancer among younger women (less than 40 years of age);[45] these gradual changes do not parallel the introduction, use, or withdrawal of DDT. The more dramatic shifts in US breast cancer incidence observed among women aged 50 and over during the last few decades have been attributed primarily to heightened public awareness and increased use of detection techniques such as screening mammography[46,47] rather than to chemical exposure. Although a true rise in incidence cannot be excluded, this increase in older women appears confined to Stage I disease without any concomitant increase in mortality.[48]

The influence of mammographic screening also hampers interpretation of increasing breast cancer rates in other industrialized nations. However, a few broad international comparisons of breast cancer incidence rates can be made. For example, although high human levels of many organochlorines have been reported from Japan, breast cancer incidence rates in that country are still low relative to those of other industrialized nations, including the US.[49] Moreover, although breast cancer incidence accelerates when Japanese women migrate to the US,[50] it is higher in second generation migrants[50] suggesting the influence of gradual changes in lifestyle.[50]

Finally, ecologic evaluations of racial and socioeconomic data are not consistent with a relationship between organochlorine exposure and breast cancer rates. In the US, the body burdens of DDT are higher among Blacks than Whites,[41,42] whereas Whites have overall higher rates of breast cancer.[49,52] DDT exposure has also been associated with lower socioeconomic status,[53] whereas breast cancer rates are elevated among higher socioeconomic groups.[51]

To date, three published formal ecologic studies[54-56] have evaluated the relationship between exposure to select organochlorine chemicals and breast cancer. The Bertazzi *et al* study[54] evaluated disease outcomes in a residential population exposed to dioxin after an industrial accident in Seveso, Italy, in 1976. The investigators compared cancer incidence rates in the exposed and in an unexposed reference population. In areas A (most highly contaminated) and B (intermediate level contamination), there was a deficit of breast cancer (11 observed *cf* 16.3 expected), but the interpretation is limited by small numbers. In zone R, an area with lower and uneven contamination, breast cancer incidence did not differ markedly from the reference rate. These findings are compatible with laboratory evidence of a reduced incidence of hormone-dependent tumors of the mammary gland among female rats exposed to TCDD.[9]

A decline in breast cancer mortality rates observed in Israel between 1976 and 1986 has been attributed to marked decreases in specific organochlorines in breast milk (DDT and lindane) noted in 1980, and decreases in BHC in cow's milk documented in 1978.[55] However, evidence for such a link is not convincing. Most of the cases contributing to breast cancer deaths observed in 1986 would have been diagnosed during the 1970s. Thus, insufficient time had elapsed (subsequent to exposure reduction) to allow for disease causation, diagnosis, and death. Also, recent decreases in Israeli breast cancer mortality rates are probably a function of migration patterns. High breast cancer mortality during the 1970s may have reflected the aging population of early immigrants from high-risk Western nations.[49] A later influx of low-risk Asian and African immigrants may have contributed to the declining rates observed in the 1980s.[57] Moreover, as discussed by Shames *et al*,[58] the Westin and Richter[55] breast cancer mortality figures are based on a single year of data and are thus unstable. An examination of the data for the five-year periods around 1976 and 1986 actually reveals a 10 percent decline in breast cancer mortality, compared with the 22 percent decrease inferred by Westin and Richter.[55]

A recent study in Long Island (New York, USA)[59] using a design with both ecologic elements and case-control structure, did not support a relationship between breast cancer and residential proximity to hazardous waste sites or contaminated wells, or sources of drinking water (municipal, well, bottled).[59] Although

recall of prior domestic use of termiticide (*i.e.*, chlordane) was poor, there was no evidence of an association with breast cancer. In a separate report, Melius[56] found no relationship between residence near industrial facilities and high motor-vehicle traffic and premenopausal breast cancer, or breast cancer risk overall. However, an increase in postmenopausal breast cancer risk was observed in Nassau County among women who had lived near chemical facilities. The type of chemical manufacturing is not specified by the authors. Moreover, it is not clear whether potential confounding factors such as ethnic group, social class, or alcohol intake, were accounted for in the analysis. Despite some methodologic limitations, the possibility that risk of postmenopausal breast cancer is increased by some unidentified pollutants arising from chemical plants[56] warrants further investigation.

Endometrial cancer. As is the case for breast cancer, international cancer trends are not consistent with an association between organochlorines and uterine cancer. Endometrial cancer rates are increasing in some populations and decreasing in others.[49] Given the established relationship between postmenopausal estrogen therapy and endometrial cancer, and the relatively brief latency of this tumor, we would expect environmental estrogen exposures to have a rapid impact on endometrial cancer rates. However, over the last two decades, there was relatively little increase in the incidence of uterine cancer among younger women in the US.[49]

Uterine cancer incidence rates in postmenopausal women underwent dramatic increases during the late 1960s, and peaked during the mid-1970s. This epidemic corresponded closely to the use of unopposed-estrogen hormone replacement therapy.[60,61] It might be argued that these increased rates reflect peak usage of DDT in the 1950s; however, endometrial cancer incidence rates fell sharply with the disuse of unopposed-estrogen therapy. If biologically persistent organochlorines had contributed to the increased endometrial cancer rates, the impact of withdrawing estrogen therapy would have been far less dramatic, and rates would have remained at least somewhat elevated relative to pre-epidemic rates.

Only the Seveso study has reported ecologic data regarding TCDD exposure and all uterine cancer (ICD-9[62] codes 179-182) incidence[54] and mortality.[63] The standard incidence ratio (SIR) on a base of 100 and relative to external incidence rates was 260 (based on two cases), 40 (two cases), and 50 (nine cases), respectively, in the areas with high, moderate, and low exposure to TCDD.[54] The standard mortality ratio (SMR) for endometrial cancer, evaluated only in the least heavily contaminated zone, was 550. Clearly, the lack of precision due to small numbers in these SIR and SMR estimates prevents any reliable conclusion.

Evidence from occupational studies

Breast cancer. Relative to the general population, exposures to organochlorines are substantially higher among workers who have direct contact with these chemicals. Occupational exposure to organochlorines has been evaluated extensively for disease and mortality outcomes, most notably soft tissue sarcomas and non-Hodgkin's lymphomas after exposure to phenoxyacetic acids and their contaminants (including TCDD).[64-66]

To date, only a few published occupational cohort studies[67-73] have evaluated breast cancer risk among women exposed occupationally to organochlorine chemicals. Lynge[67] evaluated breast cancer incidence among 1,069 women ever employed before 1982 in the chlorophenoxy herbicide industry in Denmark. Employee exposure levels were not known, but dioxin (TCDD) exposure was presumed to have occurred because the herbicides were contaminated with this chemical. Linkage to the Danish National Cancer Registry enabled complete follow-up, and national rates were used to compute expected numbers of cases. A total of 13 women were diagnosed with breast cancer, providing an SIR (per 100) of 93.

Manz *et al*[68] published cancer mortality data of an industrial cohort including 399 women employed for at least three months from 1952 through 1984 at a German herbicide plant with presumed high dioxin (TCDD) exposures. Although the TCDD body burdens of cohort members is unknown, a nonrandom survey conducted in 1985 (after the plant had closed) showed median TCDD adipose tissue levels of 60 to 137 ppt across exposure subgroups; these levels were substantially higher than general population background levels of seven to 20 ppt. Relative to German national rates, the overall cancer mortality among women was lower than expected, but a marginally significant SMR of 215 was observed for breast cancer (based upon nine deaths). In a later follow-up with one additional breast cancer death, this SMR increased to 237.[74]

Breast cancer mortality was evaluated also among 1,527 female workers in 11 occupational cohorts from seven countries,[69] classified according to the likelihood of phenoxy herbicide (TCDD) exposure. Mortality was ascertained through national records or by active follow-up; 95 percent of the population was successfully followed. Expected numbers of cancer deaths were based upon national rates. In the subgroup with certain phenoxy herbicide exposure, the SMR for female breast cancer was 30, based on one observed death. A subsequent re-analysis included incidence evaluations, and focused on the subgroup of 701 women with known

exposure to phenoxy herbicides.[70] Overall, breast cancer incidence was not elevated in this cohort (SIR = 91, based on seven cases).

Brown[71] examined the cancer mortality experience of 1,318 women employed in the heaviest PCB exposure areas of three electrical-capacitor manufacturing plants in Massachusetts and New York state. PCB exposure was not quantified for individual members of the cohort, but surveys of blood levels conducted during the 1970s among employees at one plant with exposures considered similar to those of cohort members have established substantial elevation compared with the general US population. Mortality for the cohort was determined through social security and tax records, and the National Death Index; underlying cause of death was determined from death certificates. Mortality follow-up continued through 1982. For breast cancer, an SMR of 77 was observed, based upon nine deaths.

Sinks *et al*[72] assessed outcomes (1957-86) among 846 female employees who had been exposed to PCBs at an electrical-capacitor plant in St Louis, Missouri (USA). Although breast cancer mortality was not addressed in this report, a subsequent analysis (Sinks 1994, personal communication) provided an SMR of 51 (based upon two breast cancer deaths). A report to the Ontario (Canada) Board of Workmen's Compensation[73] indicated that two breast cancer deaths (*cf* 1.99 expected) had occurred in a cohort of 1,556 female electrical-capacitor workers evaluated by Bertazzi *et al*[75] Also included in the Ontario report is a small cohort of 521 women employed at one of the electrical-capacitor plants studied by Brown[71] but not included in Brown's analysis.[76] SMRs were not computed in this report, but can be calculated as 133 for breast cancer (five deaths observed).

These reports do not support a relationship between breast cancer and occupational exposure to PCBs. The results of the phenoxy herbicide studies (TCDD) are less consistent; one study supports an association,[68] while the others do not.[67,69,70] The evaluation of breast cancer risk in occupational cohorts is frustrated by many factors, including the relatively limited numbers of women working in the chemical industry during the decades in question, and the small numbers of breast cancer cases arising in the cohorts. In addition, actual exposure levels of cohort members have not been consistently quantified. In summary, these studies share several limitations, and the results are hardly conclusive. Many of these limitations would tend to result in an underestimation of the association between organochlorines and cancer, but it is unlikely that a strong relation would have been missed if one actually did exist.

Summary analyses of the occupational studies of breast cancer. To facilitate the grasp of overall results from occupational studies of certain organochlorines and breast cancer, we have undertaken analyses to obtain a summary standardized mortality or incidence ratio from these studies. The studies were not judged as to their validity.

The observed and expected number of breast cancer cases were obtained first for each study. The summary estimate then was calculated as the ratio between the sum of the observed numbers of cases and that of the expected numbers. The aggregated estimate was weighted proportionally to the size of the cohort and its rate of breast cancer. The 95 percent confidence interval (CI) for the summary observed-to-expected ratio was obtained based on a Poisson distribution.[77] This observed-to-expected ratio (O/E ratio) should be interpreted as a relative risk estimate. Observed and expected cases were not counted twice in these analyses, but it was assumed that exposed and nonexposed cases with breast cancer have similar fatality rates.

Besides the three cohorts with possible occupational exposure to TCDD discussed in the preceding section,[67-69] Kogevinas *et al*[70] reported additional incidence experience among a subset of women from the mortality study by Saracci *et al*.[69] There was a total of 34 observed cases of breast cancer, yielding a summary O/E ratio of 1.04 (CI = 0.72-1.45) (Table 1). Excluding women who were judged to be nonexposed to TCDD in Saracci *et al*[69] (four observed cases) and those for whom TCDD exposure was judged to be unlikely in Kogevinas *et al*[70] (six cases), the summary O/E ratio was 1.08 (CI = 0.68-1.58). CI estimates in both instances were wide and included the null value of 1.0.

Similarly, four studies previously reviewed[71-73] evaluated breast cancer risk among female workers occupationally exposed to PCBs. There was a total of 18 observed cases of breast cancer, yielding a summary O/E ratio of 0.84 (CI = 0.50-1.33) (Table 2).

Endometrial cancer. Epidemiologic data of any sort regarding organochlorine exposure and endometrial cancer risk are scanty. Few occupational cohorts provided any information regarding endometrial cancer after exposure to either TCDD or PCBs. In one study,[67] two cases of endometrial cancer occurred, whereas three cases were expected, based on national rates (SIR = 67). The mortality analyses of Kogevinas *et al*[70] included an evaluation of uterine cancer (unspecified type) in a subgroup of 701 female workers with known exposure to phenoxy herbicides; an increased risk was noted (SMR = 192), but it was based on just one observed case.

Table 1. Summary analysis of occupational studies of TCDD and breast cancer

Primary author, year	Study design; exposure	O/E ratio[a]	(CI)[b]	Observed cases
Lynge, 1985[67]	Retrospective cohort	0 93	(0 50-1.60)	13
	Incidence experience of 1,069 women in chlorophenoxy herbicide industry in Denmark (1947–82);			
	TCDD			
Manz *et al*, 1991[68]	Retrospective cohort	2.15	(0.98-4.09)	9
	Mortality experience of 399 women in a herbicide plant in Germany (1952–84);			
	TCDD			
Saracci *et al*, 1991[69]	Retrospective cohort	Exposed to herbicides:		
	Mortality experience of 1,527 women	0 30	(0.004-1 67)	1
	from 11 cohorts in 7 countries;	Not exposed:		
	TCDD	1.14	(0.31-2.93)	4
Kogevinas *et al* 1993[70]	Retrospective cohort	TCDD exposure probable:		
	Incidence experience of 701[c] exposed	0 86	(0.02-4.80)	1
	women from Saracci *et al*, (1991);	TCDD exposure unlikely		
	TCDD	0.91	(0.34-1.99)	6
Summary analysis	All subjects	1.04	(0.72-1 45)	34
	Excluding subjects with unlikely or no exposure	1.08	(0.68-1.58)	24

[a] O = observed cases, E = expected
[b] CI = 95% confidence interval
[c] The 710 women in the report by Kogevinas *et al*[70] did not overlap with the women evaluated by Saracci *et al*[69]

In the study by Brown,[71] no evidence of an increase in mortality from endometrial cancer was found among the PCB-exposed workers; the SMR was 59, based on one observed case. Sinks (1994, personal communication) re-evaluated uterine cancer mortality among 846 female employees known to have been exposed to PCBs at an electrical-capacitor plant and found no deaths from uterine cancer (*cf* 0.32 expected). Similarly,

Table 2. Summary analysis of occupational studies of PCBs and breast cancer

Primary author, year	Study design; exposure	O/E[a] ratio	(CI)[b]	Observed cases
Brown, 1987[71]	Retrospective cohort	0.77	(0.35-1.46)	9
	Mortality experience of 1,318 women in electrical capacitor plants in NY and MA (1946–82);			
	PCBs			
Sinks, 1994 (personal communication)	Retrospective cohort	0.51	(0 06-1.85)	2
	Mortality experience of 846 female electrical capacitor manufacturing workers in Bloomington, IN (1957–86),			
	PBCs			
Bertazzi *et al*, 1987[74]	Retrospective cohort	1.01	(0.11-3.63)	2
	Mortality experience of 1,556 female electrical capacitor manufacturing workers in Italy (1946–82);			
	PCBs			
Nicholson *et al*, 1987[76]	Retrospective cohort	1.33	(0 43-3.10)	5
	Mortality experience of 521 female electrical capacitor manufacturing workers in NY (1946–82);			
	PCBs			
Summary analysis		0 84	(0 50-1 33)	18

[a] O = observed cases, E = expected
[b] CI = 95% confidence interval.

Bertazzi *et al*[75] reported no uterine cancer deaths (*cf* 0.77 expected) among 1,556 female workers employed at an electrical-capacitor plant.

Collectively, these occupational data are consistent with a reduced risk of endometrial cancer, perhaps due to antiestrogenic effects of dioxin. However, the small number of subjects involved severely hampers the interpretation of the results.

Case-control studies

Breast cancer. Several studies conducted since the late 1970s have addressed the concern that women exposed to chemicals such as DDT or PCBs may have higher rates of breast cancer than women not exposed to those chemicals. Five of these were case-control-like studies[78-82] and were, with one exception,[78] based on, at most, 20 cases of breast cancer; their results are subject to considerable chance variation. Also, most of these studies have examined several compounds, thus raising the issue of multiple statistical comparisons. One,[79] examining PCB and DDE, was reported as negative; the largest one[78] was considered negative with respect to PCBs and DDT/DDE but positive with respect to hexachlorocyclohexane (HCH); one[80] has been reported as positive with respect to both PCBs and DDT; a pilot study by Falck *et al*[81] showed elevated values of PCBs and p,p'-DDE in women with breast cancer; and one study[82] examining several PCB congeners and other organochlorines found higher DDE levels in estrogen receptor-positive breast cancer cases but lower levels in estrogen receptor-negative cases.

The two largest studies[83,84] thus far to evaluate the association between organochlorine compounds and breast cancer, both nested in cohorts, have not produced consistent results. Wolff *et al*[83] analyzed PCB and p,p'-DDE concentrations in sera from stored blood specimens of 58 cases and 171 controls sampled from 14,290 women enrolled in New York University Women's Health Study. Mean levels of p,p'-DDE were significantly higher (by 35 percent, or 2.7 ng/mL) in breast cancer cases than in matched control subjects. Mean levels of PCBs were 15 percent higher in cases than in controls, but the difference was not statistically significant. An elevation of serum p,p'-DDE concentrations from 2.0 ng/mL (10th percentile) to 19.1 ng/mL (90th percentile) was associated with a significant increase in the risk of breast cancer (odds ratio [OR] = 3.68, CI = 1.01-13.50). The OR per ng/mL change in PCB concentration was 1.08 and not statistically different from 1.0. This nonsignificant association was reduced further after adjustment for p,p'-DDE.

The study by Krieger *et al*[84] was a case-control study nested in the Kaiser Permanente Medical Care Program's multiphasic health examination cohort of 57,040 women in the San Francisco Bay Area (California, USA). The study population was a random sample of 50 breast cancer cases from each of three racial groups (Caucasian, African-American, and Asian) and equal numbers of individually matched controls, all of whom had blood samples stored in the late 1960s. Among all racial/ethnic groups combined, women with breast cancer and their matched controls did not differ significantly in their mean serum levels of either p,p'-DDE or PCBs. For cases and controls, respectively, mean p,p'-DDE levels were 43.3 and 43.1 ppb and mean PCB levels were 4.4 and 4.8 ppb. The authors concluded that the study did not support the hypothesis that higher serum levels of p,p'-DDE or PCBs increase the risk for breast cancer. Serum levels of p,p'-DDE did show a positive, albeit statistically nonsignificant, association with breast cancer among Caucasian and African-American women and an inverse one among Asian women. These subgroup analyses, however, do not carry the same inferential power as the overall result.

Summary analyses of the case-control studies of breast cancer.

Case-control studies with ratio of mean concentrations as the effect measure. For case-control studies, the summary ratios of the mean concentrations of organochlorines between cases and controls were derived from the weighted averages of the logarithm of the ratios from the individual studies. Weights were taken to be proportional to the inverse variance of the log ratios of the mean concentrations.

A summary analysis of the ratio of mean concentrations also has been performed by Key and Reeves.[85] Our analysis was similar, but included data from Wasserman *et al*[80] for the DDE analysis, data for deceased cases and controls from Unger *et al*[79] for the PCB analysis, and data on wet weight basis from Falck *et al*[81] for both compounds. Table 3 lists the studies included in our analyses. Results similar to those reported by Key and Reeves[85] were obtained: for DDE the summary ratio was 1.08 (CI = 0.98-1.19) and for the PCB it was 1.03 (CI = 0.96-1.10).

Case-control studies with odds ratio as the effect measure. For case-control studies which provided an OR as the effect estimate, the summary OR estimate was derived from the weighted average of the logarithm of the ORs of the individual studies. (The weighting was proportional to the inverse variance of the log OR). For studies which did not provide the log OR and its variance, the variance was derived from the reported CI estimate. We calculated the CI of the summary OR by

Table 3. Summary analysis of case-control studies with ratio of mean concentrations as the effect measure

Primary author, year Exposure	No. of cases/controls	Case Mean ± SD[a]	Controls Mean ± SD[a]	Ratio of means (CI)[b]
Wasserman *et al*, 1976[80c]				
p,p'-DDE adipose tissue	9/5	1.53 ± 1.39 ppm	4.32 ± 1.66 ppm	0.35 (0.18-0.70)
Unger *et al*, 1984[79]				
DDE biopsy cases & controls	14/21	1.23 ± 0 63ppm	1.25 ± 0.76 ppm	0.98 (0.68-1.43)
PCB biopsy cases & controls	14/21	3.89 ± 0.97	3.93 ± 1.33	0.99 (0.81-1 20)
PCB dead cases & controls	18/35	6.47 ± 2 35	5.12 ± 2.38	1.26 (1.01-1.59)
Mussalo-Rauhamaa *et al*, 1990[78]				
p,p'-DDE	41/33	0.96 ± 0 63 ppm	0.98 ± 0.89 ppm	0.98 (0.68-1.42)
PCB	41/33	1.05 ± 0.63	1.30 ± 0.75	0.81 (0.62-1.06)
Falck *et al*. 1992[81]				
p,p'-DDE (wet weight basis)	20/20	1877 ± 1283 ng/g	1174 ± 630 ng/g	1.60 (1 09-2.34)
PCB (wet weight basis)	20/20	1669 ± 894	1105 ± 424	1.51 (1.13-2.02)
Wolff *et al*, 1993[83]				
p,p'-DDE serum	58/171	11.0 ± 9.1 ng/mL	7.7 ± 6.8 ng/mL	1.43 (1.11-1.84)
PCB serum	58/171	8.0 ± 4.1	6.7 ± 2.9	1.19 (1.03-1.38)
Dewailly *et al*, 1994[82]				
DDE	18/17	1370.6 ± 2077.7 μg/kg	765.3 ± 526.9 μg/kg	1 79 (0.83-3.88)
PCB	18/17	368.1 ± 150.5	397.0 ± 161 5	0.93 (0.71-1.22)
Krieger *et al*, 1994[84]				
p,p'-DDE serum	150/150	43 3 ± 25 9 ppb	43.1 ± 23.7 ppb	1 01 (0.88-1.14)
PCB serum	150/150	4.4 ± 1.8	4.8 ± 2.5	0.92 (0.82-1.02)
Summary analysis				
DDE	—	—	—	1.08 (0.98-1.19)
PCB	—	—	—	1.03 (0.96-1.10)

[a] SD = standard deviation.
[b] CI = 95% confidence interval.
[c] Standard deviations were estimated from the ranges as described in Snedecor and Cochran,[86] pp 39-40.

taking the inverse sum of weights as the variance of the log summary OR.

Wolff *et al*[83] and Krieger *et al*[84] measured p,p'-DDE and PCB in serum samples. In addition to the mean concentrations for breast cancer cases and for controls, they provided an estimated OR associated with each unit (ppb) increase in exposure to PCB. The unit is small, and therefore, to avoid greater rounding errors in calculating the variance from the CI presented in Kreiger *et al*,[84] individual OR estimates for each ethnic group (rather than that for the total group) were used. The summary OR, presented in Table 4, was near the null value for PCB, *i.e.*, 1.02 (CI = 0.94-1.11).

For p,p'-DDE, a similar analysis which pooled estimates from Wolff *et al*[83] and from the three ethnic groups in Krieger *et al*,[84] yielded a summary OR of 1.01 (CI = 0.997-1.02) ppb increase in exposure. However, it is difficult to do a straightforward summary analysis of

Table 4. Summary analysis of two case-control studies treating serum PCB as a continuous variable and using odds ratio as the effect estimate

Primary author, year	Serum PCB		
	No. of cases/controls	OR[a] per ppb	(CI)[a]
Wolff *et al*, 1983[83a]	58/171	1.08	(0.97-1 21)
Krieger *et al*, 1994[84]			
Caucasian	50/50	0 78	(0.55-1.09)
African-American	50/50	1 06	(0.89-1.26)
Asian	50/50	0.83	(0 65-1.05)
Summary analysis	—	1.02	(0.94-1.11)

[a] Odds ratios (OR) and 95% confidence intervals (CI) were derived from the logistic regression coefficients and their standard errors.

Table 5. Mean serum p,p'-DDE levels among controls

Primary author, year	Serum p,p'-DDE Mean ± SD[a] in controls	Time lag since sample collection
Wolff *et al*, 1993[83]	7.7 ± 6.8 ng/mL	6 mos
Krieger *et al*, 1994[84]		15 yrs
Caucasian	35.0 ± 22.8 ppb	
African-American	43.4 ± 21.2 ppb	
Asian	50.8 ± 24.7 ppb	
Total	43.1 ± 23.7 ppb	

SD = standard deviation

data presented by Wolff *et al* and Krieger *et al*, since the exposure information for Krieger *et al* refers to the time period 1964-71 when levels were much higher, whereas the exposure data in Wolff *et al* refer to the time period 1985-91 when p,p'-DDE levels were substantially lower following the ban of these compounds in 1972[44] (Table 5). If this were to be ignored, then the larger exposure variation in the Krieger *et al* investigation would greatly affect the relative weight of the two studies and the overall relative risk for both studies combined would thus be almost identical to that reported by Krieger *et al*.

If DDT had a genuine effect on breast cancer risk, one could assume that the relative risk increment in the Wolff *et al*[83] study would correspond to a range of variation similar to that observed in the Krieger *et al*[84] study, rather than the range noted in their own data, in which the exponential decline of DDT/DDE over time has already occurred to a substantial extent.[44] By assuming that the range of exposure in the population studied by Wolff *et al*, if back-dated by 14 years to the time of the Krieger *et al* study, would be similar to that noted for Caucasians in Krieger *et al*, we may roughly estimate that in the Wolff *et al* study, the OR per standard deviation would be exp(22.8 ppb × 0.0823 per ppb) = 6.53. Accordingly, the ORs per standard deviation and their CIs are presented in Table 6. The summary OR was 1.27 for p,p'-DDE (CI = 0.95-1.69). It also can be seen in Table 6 that there is statistically significant heterogeneity between the four groups (χ^2 with three degrees of freedom [d.f.] = 9.98; $P = 0.02$) This heterogeneity is accounted for by the heterogeneity between Wolff *et al* and Krieger *et al*, the latter taken as a single group (χ^2 with one d.f. = 5.94; $P = 0.01$), whereas among the three ethnic groups within the Krieger *et al* study, there is no statistically significant heterogeneity (χ^2 with two d.f. = 4.02; $P = 0.13$).

Methodologic discussion regarding the case-control studies of breast cancer. The majority of the above-mentioned studies[78-82] cannot be interpreted easily, mostly because of their small sample size and their failure to control adequately for known breast cancer risk factors. Also, in several investigations, the study population was not defined clearly, raising uncertainty as to whether the selected controls were representative of the study base. Therefore, most of the reliable evidence derives from the two case-control studies nested within cohorts.[83,84]

Interpretation of these studies is not entirely straightforward, however. Recent results suggest that lactation may be a confounder of the relationship between organochlorines and breast cancer. Adjustment for duration of lactation strengthened the association between p,p'-DDE and breast cancer in the study by Wolff *et al*,[83] suggesting that longer duration of lactation was associated with higher p,p'-DDE concentrations. However, an inverse relationship between DDE levels in breast milk and duration of lactation is equally accepted.[40,87,88] This discrepancy cannot be explained at present but underlines the need for additional information on the association between duration of lactation and serum DDE levels.[89] Evidence of an inverse association between lactation and breast

Table 6. Summary analysis[a] of two case-control studies treating serum p,p'-DDE as a continuous variable and using odds ratio as the effect estimate

Primary author, year	Serum p,p'-DDE		
	No. of cases/controls	OR per standard deviation[a]	(CI)[b]
Wolff *et al*, 1993[83]	58/171	6.53	(1.70-25.07)
Krieger *et al*, 1994[84]			
Caucasian	50/50	1.25	(0.64-2.47)
African-American	50/50	1.52	(1.00-2.31)
Asian	50/50	0.78	(0.47-1.29)
Summary analysis	—	1.27	(0.95-1.69)

[a] Standard deviation (SD) of 22.8 ppb for Caucasians in Krieger *et al*.[84] was used to derive odds ratio (OR) for Wolff *et al*.[83]
[b] CI = 95% confidence interval

cancer risk independent of parity remains inconclusive, with results ranging from a weak or no association[90,91] to a definite protective effect,[92,93] at least in premenopausal women.[94]

In the study by Krieger *et al*,[84] participants were selected from a multi-racial/ethnic population, in contrast to women in other studies who were exclusively or largely Whites and/or of European descent. While mean p,p'-DDE and PCB levels were higher among African-American and Asian women than among Caucasian women, a positive association between p,p'-DDE levels and breast cancer was seen among Caucasian and African-American women but not among Asian women. Theoretically, race might be an effect modifier in studies of the relationship between organochlorines and breast cancer, although this interracial/interethnic variation also may be the result of chance.

Organochlorines such as o,p'-DDT and o,p'-DDE, have estrogenic potency close to four orders of magnitude less than the main endogenous estrogen. The hypothesis that these compounds increase the risk of breast cancer through their estrogenic action is difficult to reconcile with the inconsistent association of the more potent exogenous estrogens, such as oral contraceptives (OC) and postmenopausal hormone replacement, with breast cancer. If exogenous estrogens increase breast cancer risk, the effect of small daily doses of organochlorines would be difficult to detect in the presence of generally large doses delivered by OCs or hormonal replacement therapy (HRT).[95]

Most early investigations measured organochlorine levels among breast cancer patients only after their diagnoses. The study by Wolff *et al*[83] included only 58 cases, all of whom were diagnosed within six months of enrolling in the study. Due to this limited follow-up time, the case patients most likely had preclinical breast cancer at the time of blood sampling. In contrast, the study by Krieger *et al*[84] included a larger number of cases (150), and organochlorine levels were measured in serum collected an average of 14 years before the diagnosis of breast cancer. A change in blood or adipose concentrations of organochlorines near the time of breast cancer diagnosis, perhaps due to lipid redistribution,[96] to changes in metabolism or body weight,[97] or to breast tumor biopsy itself cannot be excluded. However, given that breast cancer usually presents with a tumor of 20 mm or less in diameter,[98] and that empirical evidence regarding weight loss or metabolic changes during the early stages of breast cancer is currently lacking, it seems unlikely that a tumor burden of only a few grams could significantly affect organochlorine levels.

There are some difficulties in the interpretation of the DDT levels. Women in the study by Krieger *et al*[84] were enrolled prior to the federal restrictions on the use of DDT, which, together with differences in geography and socioeconomic status, most likely accounts for the four to five times higher mean p,p'-DDE levels in this study than in the study by Wolff *et al*.[83] MacMahon[99] has suggested that an association between DDT and its metabolites and breast cancer would be more likely to be observed in women whose sera were sampled many years earlier (closer to the induction time of breast cancer), as opposed to within six months of breast cancer diagnosis. The use of p,p'-DDE as a marker may be questionable given its absence of estrogenic activity relative to o,p'-DDT and o,p'-DDE. While the measurements in the Krieger *et al* study may reflect recent exposure to technical DDT containing the weakly estrogenic o,p'-DDT and o,p'-DDE, the measurements in the Wolff *et al* study may largely reflect exposure to p,p'-DDE itself derived from recent food consumption.

The limited sample size of most of the epidemiologic studies does not permit evaluation of the possibility that the risk attributed in some studies to organochlorines simply may be a surrogate for other dietary aspects that contribute to organochlorine accumulation in the body. Since epidemiologic evidence of a relation between dietary fat intake and breast cancer is not strong,[100] and dietary fat is the primary source of human organochlorine exposure, an indirect link between fat-soluble organochlorine compounds and subsequent breast cancer risk through dietary fat consumption seems unlikely.[97]

The most likely explanation for the inconclusive epidemiologic findings regarding the association between organochlorines and breast cancer is that these compounds, at the levels they are currently encountered, are too weak to show any effect, although a balance between estrogenic and antiestrogenic responses to individual compounds cannot be excluded. For example, the biologic activity and toxicity of both PCBs and PCDDs are known to be specific to the structure and/or degree of chlorination of the individual congener. Only 60 to 70 of the 209 PCB congeners have been identified in humans, and the 20 congeners which represent the total value commonly reported in epidemiologic studies include both estrogenic and antiestrogenic compounds.[101]

Discussion

Many of the compounds covered in this review are established animal carcinogens, largely leading to carcinomas and adenomas of the liver. In theory,

these compounds could affect the risk of estrogen-related cancers through nonhormonal mechanisms, but the prevailing hypothesis is that their hormonal actions are the relevant ones.[102] However, effects on tumor incidence in estrogen-dependent targets rarely have been observed in animals, the most notable exception being TCDD, which appears to reduce mammary tumor incidence.[9] 'DDT' (purity not specified) and o,p'-DDT have been shown, in animal studies, to accelerate the growth of mammary tumors.[34,103] However, p,p'-DDT also has been shown to decrease DMBA-induced mammary tumor incidence.[35] These chlorinated compounds, in general, are devoid of any genotoxic actions and are presumed to act in the animal systems as tumor promoters.

These organochlorine compounds occur as a background exposure in the general population, in a mixture that is similar in composition in different areas of the industrialized world, except when local contamination has occurred. Any possible estrogenic effect therefore, may be related to the total impact of this mixture, *i.e.*, both the estrogenic and antiestrogenic components. The lack of data comparing their relative estrogenic potency under realistic conditions, makes such a determination difficult.

In the epidemiologic study by Wolff *et al*,[83] blood was sampled from the women during the period 1985-91 and analyzed for p,p'-DDE and PCB. The DDE level in the case patients was 11.0 ± 9.1 ng/ml (mean $\pm$ SD). The intake of total DDT (of which p,p'-DDE constitutes the major part) at that time has been calculated by Vaz[104] based on figures from US Food and Drug Administration (1990) and estimated to be in the range of 10 to 77 ng/kg bodyweight per day. Even if intakes during the preceding years had been considerably higher, they were still about six orders of magnitude below those which caused tumor promotion in animal studies[34,103] (25-30 mg/kg bodyweight and day).

From the data available, it is clear that organochlorine contaminants potentially relevant to humans are a diverse group of chemicals that, at certain dose levels, could affect human steroid hormone systems in several ways. With regard to estrogen-related events, certain of these compounds act as estrogens, while others act as antiestrogens. The final outcome of this mixed environmental exposure will depend on the balance between these actions. At present there are no biologic, toxicologic, or analytic data available that can be utilized to indicate that there would be a dominance one way or the other, or that exposure levels that can affect human cancer risk have been achieved in any but the most unusual situations.

The hypothesis that human exposure to environmental levels of organochlorines would favor an estrogenic overactivity leading to an increase in estrogen-dependent formation of mammary tumors is not supported by the existing *in vitro* and animal evidence but, in epidemiologic terms, neither can it be rejected on the basis of this evidence. In reality, however, it is questionable whether the background levels of organochlorines in the general population will be high enough to elicit any of these effects. In fact, the crude comparisons made above would indicate that this is unlikely. Further, this question must also be addressed in relation to the exposure to generally occurring natural estrogenic compounds in the food.

The epidemiologic data in this context are no more informative. Since the organochlorines are only weak estrogens or antiestrogens, one has to consider much stronger endogenous or exogenous estrogenic stimuli, as well as the possible competition for estrogen receptors. OCs and menopausal estrogen treatment, for example, are likely to have much more pronounced hormonal effects, albeit more time-limited. The epidemiologic difficulty is then to discern in women the effects, if any, of weak, but prolonged, estrogenic or antiestrogenic exposure in the likely presence of intermittent stronger hormonal influences. Moreover, the chemicals considered are all lipid-soluble, and reach human tissues predominately through the diet; they will tend to be ingested together, perhaps in certain types of foods. Thus, the body burdens of many organochlorines are likely to be inter-correlated, and related as well to other lipid-soluble substances and to diet. This will complicate attempts to disentangle the independent effects, if any, of these exposures.

Future research

Experimental research

To estimate the estrogenic (and/or antiestrogenic) load in humans from all external exposures, it is necessary to develop efficient methods to determine estrogenic potency. These preferably should be simple *in vitro* techniques with *in vivo* validation. Data from such potency measurement can be used to estimate human exposure in various groups participating in epidemiologic studies.

A number of potentially useful *in vitro* methods are available. Perhaps the most promising is the modification of cell lines or microorganisms by the techniques of modern molecular biology. The organisms can be transfected with an estrogen-dependent reporter gene, expressed only when the estrogen receptor is activated. Techniques are available to incorporate different human steroid-receptor genes and different reporter genes such as LacZ, CAT or luciferase. Receptor activation can be measured indirectly by the activity of the reporter gene,

often through an enzyme. The evaluation is done by estimating the number of colored cells after addition of the enzyme substrates. Consequently, this kind of system will be sensitive and easy to use.

An alternative approach may be to use established human-breast cell lines sensitive to estrogen-mediated cell growth, *e.g.*, MCF-7, which requires estrogen for optimal cell division. In addition, this cell line could be used in combination with reporter genes such as CAT or luciferase in order to increase the sensitivity.

Even if the use of genetically manipulated cell lines will increase the possibility of identifying compounds with estrogenic activity, there will remain a need for the development of *in vivo* assays to validate such systems.

Epidemiologic research

With respect to DDT/DDE, nested case-control studies, similar in design to those undertaken by Wolff *et al*[83] and Krieger *et al*[84] and focusing on endometrial as well as breast cancer, represent an obvious priority. More traditional case-control studies, with exposure assessment through biologic samples taken concurrently with diagnosis of cancer and control ascertainment, also may provide valid information. This is because early-stage breast cancer and, conceivably, endometrial cancer are not known to have systemic metabolic effects substantial enough as to introduce information bias. Measurement of, and adjustment for, blood lipids should be considered in such studies. Undertaking of analytic epidemiologic investigations with proxy indicators of exposure (*e.g.*, residential or occupational history) and of properly conceptualized and interpreted ecologic studies may be of some use, but their results are unlikely to be of critical importance.

For other organochlorine compounds, the options, in declining order of preference, are: (i) if a persistent biomarker exists or can be identified, case-control studies could be undertaken; (ii) in the absence of an appropriate biomarker, occupationally or accidentally exposed groups could be studied through retrospective cohort designs.

With epidemiologic methods, it is always difficult to study weak ssociations and almost impossible to exclude such associations. Moreover, if some organochlorine compounds were suspected as having health effects mediated through their estrogenicity, it appears unlikely that such effects would be demonstrable in women; this should be obvious by comparing the estrogenicity of estradiol, the principal endogenous estrogen, and that of the suspected organochlorine compounds. A substantial amount of epidemiologic work nevertheless is underway to accommodate the current concern that certain organochlorine compounds cause cancer in women. Endometrial cancer is related much more strongly and unequivocally to exogenous estrogens than breast cancer.[105] We strongly suggest therefore that the focus of future research is shifted from breast to endometrial cancer, because the latter is likely to be a more sensitive marker of weak estrogenic effects.

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